REMARKS

Status of the Claims

Pending claims

Claims 42 to 55, 93 and 94 are pending.

The Restriction Requirement

The Patent Office alleged that the pending claims of the application are directed to ninety separate and distinct inventions under 35 U.S.C. §121:

Group I: Claims 1-23, 40-41, 67-85 drawn to DNA, vectors, hosts cells, probes and expression of transaminase, classified in class 435, subclass 193.

Group II: Claims 24-35, 64, 86-87 drawn to transaminases, classified in class 435, subclass 193.

Group III: Claims 36-39, drawn to transaminase antibodies, classified in class 530, subclass 387.9.

Group IV: Claims 42-55, drawn to methods of generating a variant polynucleotide, classified in class 435, subclass 440.

Group V: Claims 56-60, drawn to a computer and computer readable medium, classified in class 712, subclass 1.

Group VI: Claims 61-63, drawn to methods of computer analysis of polynucleotide sequences, classified in class 700, subclass 90.

Group VII: Claim 65, drawn to a method of using a transaminase, classified in class 435, subclass 168.

Group VIII: Claim 66, drawn to methods of identifying variant polypeptides, classified in class 435, subclass 27.

Group IX: Claims 88-92, drawn to a method of modifying small molecules, classified in class 435, subclass 41.

The Patent Office further alleged that for each of inventions I-IX, restriction to one of the following is also required under 35 U.S.C. §121, inventions (A)-(J), SEQ ID NOS:17-24, 35 and 39, a sequence encoding thereof, or an antibody against it and methods of making and using thereof, respectively.

In response to the Restriction Requirement, Applicants elected Group IV, nucleotides group G, claims 42-55, drawn to methods of generating variants of SEQ ID NO:23, or a polynucleotide encoding SEQ ID NO:31, with traverse.

Applicants respectfully submitted that the Patent Office should reconsider and allow the rejoinder of nucleotide groups A, B, C, D, F, and J, all transaminases originally derived from the organism *Aquifex*.

Claims amended and added in the instant amendment

In the present response, claims 42, 43, 55, 93 and 94 are amended, new claims 95 to 104 added. Accordingly, after entry of the instant amendment, claims 42 to 55 and 93 to 104 are pending and under examination.

Outstanding Rejections

Claims 42 to 55, 93 and 94 are rejected under 35 U.S.C. §112, first and second paragraphs. Claims 42 and 93 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Henner, et al. (1986) Gene 49:147-152 (hereinafter "Henner"). Claims 42 to 55, 93 and 94 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Henner in view of Short, U.S. Patent No. 5,939,250, issued August 17, 1999, filed May 22, 1996 (hereinafter "Short"). Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

Support for the claim amendments can be found throughout the specification. For example, support for claims directed to methods for generating variants of parent nucleic acids having various sequence identities to exemplary sequences of the invention can be found, inter alia, in paragraph 58, page 11, and paragraph 229, page 56, of the specification. Accordingly, Applicants respectfully submit that no new matter is introduced by the instant amendments.

Information Disclosure Statement

A clean Form PTO 1449 is attached to supplement the Information Disclosure Statement submitted July 12, 2001.

Objections to the specification

The disclosure is objected to for various informalities:

On page 6, paragraph 36, the erroneous term "*Aquifex degensii*" has been replaced with the correct term "*Ammonifex degensii*".

The specification is objected to because of the definition of the term "substantially identical." The instant amendment addresses this issue.

The specification is objected to because of the term "GSSM". The instant amendment addresses this issue.

Objections to the specification

Claims 43, 49 and 94 are objected to because of a misspelling of "in vivo." The instant amendment addresses this issue.

Claims 42 to 55, 93 and 94 are objected to under 37 CFR 1.75(d)(1). The instant amendment addresses this issue.

Issues under 35 U.S.C. §112, first paragraph

Written Description issues

Claims 42 to 55, 93 and 94 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the art that the inventors at the time the application was filed had possession of the invention. In particular, it is alleged that because the variant nucleic acid generated by the claimed methods do not have a function and can be any number of possible modifications of the parent nucleic acid, the claims are drawn to a method of generating a genus of variants of any structure and function. It is noted that the specification teaches the structure of a single representative species, SEQ ID NO:23, encoding a histidinol phosphate aminotransferase.

The instant amendment addresses this issue. The claimed methods as amended generate variant nucleic acids encoding polypeptides having a transaminase activity. Thus, the amended claims methods are drawn to generating a genus of variants of specific structure and function, i.e., nucleic acids encoding polypeptides having a transaminase activity.

Applicants respectfully submit that the claimed invention is sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. Applicants respectfully submit that describing a genus of polynucleotides in terms of its physico-chemical properties (e.g., sequence identity) and function (e.g., encoding a polypeptides having a transaminase activity) satisfies the written description requirement of section 112, first paragraph.

Applicants respectfully refer to the USPTO guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph. In example 14 of the guidelines (a copy of which is attached as Exhibit A), a claim reciting variants claimed by sequence identity to a sequence is sought (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B). In the example, the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions. Procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and an assay is described which will identify other proteins having the claimed catalytic activity. The analysis of example 14 states that procedures for making variants (which have 95% sequence identity) are conventional in the art. The Guidelines conclusion states that the disclosure meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention.

Analogously, the genus of nucleic acids used in the claimed methods is described by structure (the exemplary nucleic acid SEQ ID NO:23, or encoding SEQ ID NO:31), a physico-chemical property (percent sequence identify) and function (having a transaminase activity). All nucleic acids of the genus used in the claimed methods must have at least 70% or more sequence identity to a sequence as set forth SEQ ID NO:31 or SEQ ID NO:23. The USPTO guidelines recognize that written description is met for a genus of polypeptides described by structure, a physico-chemical property (e.g., a % sequence identity) and a defined function, the genus of claimed polypeptides also meet the written description requirements of section 112.

The genus of nucleic acids used in the claimed methods also fully comply with the requirements for written description of a genus of nucleic acids as set forth in University of California v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed. Cir. 1997). In Lilly, the Court stated that, "[a] description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs....*or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*" (emphasis added) Lilly, 43USPQ2d at 1406. As noted above, the instant claims clearly set forth specific structural and physical characteristics of the claimed polymerase-encoding nucleic acids. The claimed genus of polypeptides all must have a polymerase activity and a specific physical characteristic, e.g., a % sequence identity to the exemplary nucleic acid. Therefore, the genus of nucleic acids used in the claimed methods is defined via shared physical and structural properties in terms that "convey with reasonable clarity to those skilled in the art that Applicant, as of filing date sought, was in possession of invention." (Vas-Cath Inc. V. Mahukar, 19 USPQ2d 1111, (Fed Cir. 1991)).

More recently, the Federal Circuit stated

Similarly, in this court's most recent pronouncement, it noted:

> More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, 314 F.3d at 1332 [Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)].

Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. LEXIS 6285; Fed. Cir. 01-1063, -1083, April 1, 2003.

Analogously, the function of the transaminases encoded by the nucleic acids generated by the claimed methods is sufficiently correlated to a particular, known structure (the exemplary sequences) and a physical (physico-chemical) property (percent sequence identity). Accordingly, the sequences used in the claimed methods are defined via shared physical and structural properties in terms that convey with reasonable clarity to those skilled in the art that

Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

Applicants also respectfully refer to recently issued claims directed to genuses of polynucleotides based on sequence identity (and stringent hybridization) to an exemplary nucleic acid, see, e.g., recently issued claims directed to, e.g., 72.5% sequence identity, as in USPN 6,593,514; 75% sequence identity, as in USPN 6,586,215; 80% sequence identity, as in USPN 6,596,926; 85% sequence identity, as in USPN 6,590,141 and USPN 6,586,179; 86% sequence identity, as in USPN 6,583,337; 90% sequence identity (and "stringent hybridization"), as in USPN 6,541,684 (see Exhibit B).

Accordingly, Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C. §112, first paragraph

Claims 42 to 55, 93 and 94 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

The phrases "obtaining a nucleic acid ..." and "fragments comprising ..."

The Patent Office has concerns with the phrasing of claim 42. The instant amendment addresses this issue.

The phrase "substantially identical"

The Patent Office has concerns with the phrase "substantially identical" in claim 42. The instant amendment addresses this issue.

The term "complementary"

The Patent Office has concerns with the term "complementary" in claim 42. The instant amendment addresses this issue.

Issues under 35 U.S.C. §102

Henner, et al. (1986) Gene 49:147-152

Claims 42 and 93 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Henner.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

The Patent Office alleges that Henner teaches a sequence 50% identical to a fragment of at least 30 or 100 nucleotides of SEQ ID NO:23.

The instant amendment addresses this issue. After entry of the instant amendment, the claimed methods generate a variant nucleic acid encoding a polypeptide having a transaminase activity by modifying the sequence of a nucleic acid comprising (i) a sequence encoding a polypeptide having an aminotransferase activity and having at least 50% sequence identity to SEQ ID NO:31, or a nucleic acid having at least 50% sequence identity to SEQ ID NO:23 encoding a polypeptide having an aminotransferase activity, (ii) sequences complementary to (i), (iii) a sequence comprising at least 30 consecutive nucleotides of a sequence encoding a polypeptide having an aminotransferase activity and having at least 60% sequence identity to SEQ ID NO:31, or a nucleic acid having at least 60% sequence identity to SEQ ID NO:23 encoding a polypeptide having an aminotransferase activity, or (iv) a sequence comprising at least 30 consecutive nucleotides of sequences complementary to (iii).

Issues under 35 U.S.C. §103

Henner in view of Short

Claims 42 to 55, 93 and 94 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Henner in view of Short.

The Patent Office alleges that Henner is defective in that it does not teach the methods of mutagenesis specifically recited in claims 43 to 55.

However, Applicants respectfully aver that Henner is further defective in that it does not teach the sequences modified in the claimed methods. As noted above, after entry of the instant amendment, the claimed methods generate a variant nucleic acid encoding a

polypeptide having a transaminase activity by modifying the sequence of a nucleic acid comprising (i) a sequence encoding a polypeptide having an aminotransferase activity and having at least 50% sequence identity to SEQ ID NO:31, or a nucleic acid having at least 50% sequence identity to SEQ ID NO:23 encoding a polypeptide having an aminotransferase activity, (ii) sequences complementary to (i), (iii) a sequence comprising at least 30 consecutive nucleotides of a sequence encoding a polypeptide having an aminotransferase activity and having at least 60% sequence identity to SEQ ID NO:31, or a nucleic acid having at least 60% sequence identity to SEQ ID NO:23 encoding a polypeptide having an aminotransferase activity, or (iv) a sequence comprising at least 30 consecutive nucleotides of sequences complementary to (iii).

Accordingly, Henner in view of Short does not teach or suggest the claimed invention.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs and 35 U.S.C. §102(b) and §103(a). Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If necessary, please apply additional and necessary charges, and apply all credits, to Deposit Account No. 06-1050.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: Aug 11, 2003

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